

REMARKS/ARGUMENTS

Status of the claims

Claims 38, 40, 43, 44, and 45 have been amended. Claim 38 has been amended to correct a typographical error and to incorporate the limitations of claim 42. Further support for the amendment to claim 38, and for claim 45, may be found, for example, at page 15, paragraph [0060]. Claim 44 has been amended for clarity as suggested by the Examiner. Claims 39 and 42 have been canceled. Claims 40 and 43 have been amended to correct dependencies based on the cancellation of claims 39 and 42. New claims 75-78 have been added. Support for new claims 75-78 may be found in previously presented claims 38, 40, 41, and 43, and in the specification, for example, at page 15, paragraph [0060]. Thus, no new matter has been added. Upon entry of this amendment, claims 38, 40-41, 43-53, and 75-78 are pending for examination in this application. Reconsideration is respectfully requested.

Restriction requirement

Applicants acknowledge the Examiner's decision to make the restriction requirement final. Applicants expressly reserve the right under 35 U.S.C. § 121 to file a divisional application directed to the nonelected subject matter during the pendency of this application or an application claiming priority from this application.

Claim objections

Claim 38 stands objected to for the typographical error in the spelling of "comprising". Applicants thank the Examiner for bringing this to the Applicants' attention, and an appropriate correction has been made.

Claim 44 stands objected to because the phrasing of "the claim does not necessarily require the transgenic eukaryotic host to comprise the same expression vector as the feed or feed additive." *See* Office Action at page 3. To improve clarity, claim 38 has been amended along the lines suggested by the Examiner.

In view of the foregoing claim amendments, Applicants respectfully request withdrawal of the objections to the claims.

Claim rejections under 35 U.S.C. § 101

Claim 44 stands rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. Specifically, the Examiner alleges that claims directed to "transgenic eukaryotic hosts" can include humans. Claim 44 has been amended to recite "transgenic yeast", thus obviating this ground for rejection.

Claim rejections under 35 U.S.C. § 112, first paragraph, written description

Claims 38-53 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. To the extent that this rejection applies to the amended claims, Applicants respectfully traverse. In making this rejection, the Examiner alleges that there is a lack of written support in the specification for the genus of vitellogenin genes.

1. The term "vitellogenin" has an art accepted meaning

Underlying the Examiner's rejection is the allegation that "the specification does not disclose the normal biological function for each of the vitellogenins identified in the art at the time of the invention". See Office Action at page 5. The Examiner then cites a number of diverse proteins, including vitellogenin, DSC-4 (defecation suppressor of clk-1), APOB (apolipoprotein B), apolipophorin I, apolipophorin II, and MTP/Mttp (microsomal triglyceride transfer protein) as being examples of vitellogenins, based on these proteins having a common amino-terminal "vitellogenin domain". See Office Action at page 5. Based on this supposed heterogeneity among vitellogenins, the Examiner concludes that "the known vitellogenins are not functionally equivalent and the breadth of their respective "biological functions" are not known." See Office Action at page 5.

a) Legal standards

The MPEP states that "[i]nformation which is well known in the art need not be described in detail in the specification." See MPEP § 2163(II)(A)(2) (citing to *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80 (Fed. Cir. 1986) ("Furthermore, a patent need not teach, and preferably omits, what is well known in the art.") The MPEP further states that "[t]he description need only describe in detail that which is new or not conventional." See MPEP § 2163(II)(A)(3) (also citing to *Hybritech, Inc.* at 1379-80).

Furthermore, with reference to nucleic acid or protein sequences, the Federal Circuit has held that known nucleotide sequences need not be recited in a patent specification to meet the written description requirement if such sequences are publicly available as of the filing date. *See Falko-Gunter Falkner v. Inglis*, (Interference No. 105,187, Docket No. 05-1324). Specifically, the Federal Circuit held:

[A] requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. . . . Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly, we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences. *See Falkner* at pages 17-18.

b) The meaning of "vitellogenin" is well known to those of skill in the art

Applicants respectfully submit that the term vitellogenin is not new or unconventional and has an art accepted meaning that is readily understood by a person of skill in the art. As defined by Brandt *et al.* (BioEssays 27: 339-346 (2005), as cited by the Examiner), "vitellogenin is a very high-density protein produced by egg-laying animals (insects, nematodes and vertebrates) as a yolk precursor protein." (Emphasis added.) *See Brandt et al.* at page 342. Furthermore, the Oxford Dictionary of Biochemistry and Molecular Biology characterizes vitellogenin as the precursor protein of lipovitellin and phosphitin in the vertebrate egg laying organisms, *Xenopus* and chickens. *See Oxford Dictionary*, revised edition, 2000, at page 685. Furthermore, vitellogenins are also known to be expressed in fish, another egg laying species, where, for example, it is used experimentally as a biomarker for environmental estrogens and other endocrine disrupting substances. *See, e.g., Heppell et al., Environ Health Perspect* 103(Suppl 7):9-15 (1995). Thus, the normal biological function of "vitellogenin", as a phospholipoglycoprotein precursor to egg yolk in egg laying animals, is implicit in its art accepted name, and this function would be so recognized by the skilled artisan. Accordingly, many of the diverse proteins cited by the Examiner as contributing to the lack of "functional

equivalency" and "undefined breadth" of the term vitellogenin (*e.g.*, apolipoprotein B, apolipophorin I, apolipophorin II, and MTP/Mttp (microsomal triglyceride transfer protein)), are expressed in non-egg laying mammals, and are not, in fact, vitellogenins. The mere fact that these mammalian proteins share some limited degree of homology with vitellogenins, such as those found in fish or birds, does not make them vitellogenins, as this term is generally understood in the art. By analogy, the fact that a number of cell surface proteins, such as receptor tyrosine phosphatases and cytokine receptors, have fibronectin type repeats does not make these proteins fibronectins.

2. A sufficient representative number of vitellogenin species is disclosed in the specification to satisfy the written description requirement

In making this written description rejection, the Examiner correctly notes that "[i]n analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure." The Examiner further admits that SEQ ID NOs: 1-20 disclose the complete structure of nucleic acid species encoding vitellogenin. However, the Examiner then alleges that "[t]he Applicant has not provided any description or reduction to practice of nucleic acids encoding a vitellogenin polypeptide besides SEQ ID NOs: 1-20", and thus, "Applicant is [not] in possession of the broad genus of vitellogenin genes". See Office Action at page 7.

As alluded to by the Examiner, the *Eli Lilly* case sets forth a standard for adequate written description of a genus, stating, in part, that "[a] description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus . . .". (Emphasis added.) See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

Furthermore, the Examiner has also pointed to The Revised Interim Guidelines as stating that "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" . . . "adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". One common denominator of the case law and guidelines put forward by the

Examiner is the proposition that the disclosure of a single sequence may not be sufficient to provide written description for a genus.

Applicants agree with the Examiner that the complete structures of 20 vitellogenins are disclosed in the specification. Accordingly, Applicants respectfully submit that the explicit disclosure of 20 structures, in combination with the known function of these proteins as egg yolk precursor proteins, provides a representative number of structures that constitutes more than adequate written description for the genus of vitellogenins as required by the case law and guidelines cited by the Examiner.

Furthermore, Applicants direct the Examiner's attention to page 7, paragraph [0032], of the present specification that states "[v]itellogenin gene and protein sequences are known and publicly available, for example from the GenBank database". A search of the GenBank protein sequence database at the NCBI website using the term "vitellogenin" results in 771 protein sequences. Applicants respectfully submit that the complete structures embodied in these 771 sequences provides an overwhelming additional number of representative species to satisfy the requirements for adequate written description as set forth in the case law and examination guidelines cited by the Examiner.

Accordingly, with respect to claims 45 and 75, because the specification provides explicitly the complete structures of 20 sequences, and guidance for obtaining at least 700 more structures, Applicants submit that more than adequate written description for the genus of vitellogenin proteins is provided in the specification. Thus, Applicants respectfully request withdrawal of this ground for rejection.

With respect to claim 38, this claim has been amended to recite the sequence of SEQ ID NO: 1, which the Examiner has found to be adequately described in the specification and free of the prior art, thus obviating this ground for rejection with respect to claim 38 and its dependent claims.

3. Written description of the term vitellogenin "gene"

With respect to the Examiner's objection that "a claimed cDNA nucleic acid does not read on a genomic sequence because full-length cDNAs would not be expected to contain introns or transcriptional regulatory elements such as promoters and enhancers that are found in

genomic DNA" (*see* Office Action at page 5), Applicants have amended the claims to recite "cDNA", thus obviating the grounds for rejection based on this objection.

Claim rejections under 35 U.S.C. § 112, first paragraph, enablement

Claims 38-53 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

In making this rejection, the Examiner states that "the specification, while being enabling for a transgenic yeast comprising an expression vector, wherein said expression vector comprises a vitellogenin gene operably linked to a promoter functional in yeast, does not reasonably provides enablement for an enormous genus of transgenic eukaryotic organisms." *See* Office Action at page 7. The Examiner has helpfully indicated that "limiting the claimed invention to a transgenic yeast comprising an expression vector, wherein said expression vector comprises a vitellogenin gene operably linked to a promoter functional in yeast, is proper." *See* Office Action at page 14.

Applicants have amended claims 38 and 44, and added new claim 75, along the lines suggested by the Examiner to recite "yeast" or "transgenic yeast". Furthermore, pending claim 45 already contains the language which the Examiner has deemed to be proper. Accordingly, Applicants respectfully request withdrawal of this ground for rejection.

Claim rejections under 35 U.S.C. § 102

To anticipate a claim, a reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found... in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

A. Claims 38 and 44 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Yan *et al.* (Developmental Biology 140: 281-290 (1990)) ("Yan"). To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

The Examiner characterizes Yan as teaching "transgenic flies comprising an expression vector comprising a vitellogenin gene operably linked to a promoter, wherein the promoter is functional in a eukaryotic host, specifically a fly." *See* Office Action at page 14.

Applicants have amended claims 38 and 44, and added new claim 75, to recite "yeast" or "a transgenic yeast"; thus, these claims do not read on a transgenic fly as taught by Yan. Accordingly, Yan does not teach or suggest each and every element of the claimed invention as required for anticipation, and Applicants respectfully request withdrawal of this ground for rejection.

B. Claims 38 and 44 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Grant *et al.* (Mol. Biol. Cell 10: 4311-4326 (1999)) ("Grant"). To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

The Examiner characterizes Grant as teaching "transgenic worms comprising a vitellogenin gene operably linked to a promoter, wherein the promoter is functional in a eukaryotic host, specifically a worm." *See* Office Action at page 14. Applicants have amended claims 38 and 44, and added new claim 75, to recite "yeast" or "a transgenic yeast"; thus, these claims do not read on a transgenic worm as taught by Grant. Accordingly, Grant does not teach or suggest each and every element of the claimed invention as required for anticipation, and Applicants respectfully request withdrawal of this ground for rejection.

C. Claims 38-39 and 44-45 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Bradbury *et al.* (J. Biol. Chem. 274:3159-3164 (1999)) ("Bradbury"). To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

The Examiner alleges that Bradbury teaches "the generation of transgenic yeast comprising an expression vector comprising a vitellogenin gene, specifically microsomal triglyceride transfer protein (MTP), wherein the nucleic acid comprising said MTP gene is operably linked to a promoter that is functional in yeast." *See* Office Action at page 15. Applicants respectfully submit that despite the fact that "ApoB and MTP . . . share a common ancestry with the vitellogenins of nematodes" (Bradbury at page 3159), MTP is not a vitellogenin as alleged by the Examiner. Applicants, for example, direct the Examiner to Figure 1 on page 344 of the Brandt review article cited by the Examiner (Brandt *et al.*, BioEssays 27: 339-346 (2005). Figure 1 in Brandt indicates that MTP and ApoB are proteins distinct from vitellogenins. Furthermore, Bradbury discloses the sequence of MTP from humans. As discussed above, vitellogenin is an egg yolk precursor protein not found in humans. Thus,

contrary to the Examiner's allegation, Bradbury cannot teach or suggest a transgenic yeast comprising a vitellogenin gene. For these reasons, Bradbury does not teach or suggest each and every element of the claimed invention as required for anticipation, and Applicants respectfully request withdrawal of this ground for rejection.

D. Claims 38-39 and 44-46 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Nusbaum *et al.* (Nature Genetics 22:388-393 (1999)) ("Nusbaum"). To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

In making this rejection, the Examiner characterizes Nusbaum as teaching "the generation of transgenic yeast comprising yeast artificial chromosomes comprising segments of the mouse genome [YAC clones]." The Examiner further alleges that "absent evidence to the contrary, one of ordinary skill in the art would reasonably expect and/or conclude that at least one YAC clone comprises at least one murine vitellogenin gene because Nusbaum *et al.* teach the YAC library to cover approximately 92% of the mouse genome." *See* Office Action at page 16. Similarly to the discussion above, mice do not contain vitellogenin genes within their genomes, and thus, none of the YAC clones taught by Nusbaum could comprise a murine vitellogenin gene, as suggested by the Examiner. For at least this reason, Nusbaum does not teach or suggest each and every element of the claimed invention as required for anticipation, and Applicants respectfully request withdrawal of this ground for rejection.

E. Claims 38-40 and 44-46 stand rejected under 35 U.S.C. § 102(a) and 102(e) as being allegedly anticipated by Jacobs *et al.* (U.S. 2001/0039335A1) ("Jacobs"). To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

In making this rejection, the Examiner characterizes Jacobs as disclosing "a polypeptide having similarity to chicken vitellogenin, wherein said polynucleotide may be expressed heterologously in yeast cells". *See* Office Action at page 16. Applicants respectfully submit that because Jacobs discloses sequences derived from human cells, Jacobs cannot teach or suggest a vitellogenin gene for the reasons discussed above. Accordingly, Jacobs does not teach or suggest each and every element of the claimed invention as required for anticipation, and Applicants respectfully request withdrawal of this ground for rejection.

Claim rejections under 35 U.S.C. § 103

Claims 38-41 and 44-53 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Cregg *et al.* (Molecular Biotechnology 16: 23-52 (2000)) ("Cregg") and Bradbury. To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations." All three elements set forth above must be present in order to establish a *prima facie* case of obviousness.

In making this rejection, the Examiner cites Cregg for its teaching of the expression of more than 200 different heterologous proteins in the yeast *P. pastoris* and some of the advantages of this system for protein expression. The Examiner acknowledges that Cregg does not teach yeast expressing a vitellogenin gene. *See* Office Action at page 17. The Examiner alleges that Bradbury teaches "the generation of transgenic yeast comprising an expression vector comprising a vitellogenin gene, specifically microsomal triglyceride transfer protein (MTP)", and that it would be obvious to express the MTP protein of Bradbury in the expression system of Cregg to arrive at the presently claimed invention. The Examiner further alleges that although SEQ ID NO:1 is not disclosed by either Cregg or Bradbury, it would be obvious to express the vitellogenin gene of SEQ ID NO: 1 in yeast. *See* Office Action at pages 17-18.

One of the requirements to establish a *prima facie* case of obviousness is that the references, alone or in combination, must teach each and every element of the claimed invention. As discussed above, the MTP protein of Bradbury is not a vitellogenin, and thus, this element of the claimed invention is not taught by the cited references. Furthermore, as acknowledged by the Examiner, the cited references do not disclose SEQ ID NO: 1, now an element of claim 38.

Thus, the cited references, alone and in combination, fail to teach each and every element of the claimed invention as required to establish a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and request withdrawal of this rejection.

Claims free of prior art

Applicants thank the Examiner for pointing out that claims 42-43 comprising the nucleic acid sequence of SEQ ID NO:1 encoding a vitellogenin polypeptide are free of the prior art. Applicants have made appropriate claim amendments based on this finding by the Examiner.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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